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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,801	12/10/2004	Stuart James Broughton	PG4860	8957

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EXAMINER	
GRAFFEO, MICHEL	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 02/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/517,801	BROUGHTON ET AL.	
	Examiner	Art Unit	
	Michel Graffeo	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,16 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,16 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8 Dec 05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Action

Claims 1-10 and 16-17 are pending and examined.

Applicant has amended claims 9-10, canceled claims 11-15, added new claim 17 and provided arguments for the patentability of claims 1-10 and 16-17 in the response filed 8 December 2005.

Applicant's arguments, see response, filed 8 December 2005, have been fully considered and are not persuasive. Any rejection not specifically stated in this Office Action has been withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 17 is rejected under 35 U.S.C. 112, first paragraph, because the specification and prior art, while contributing to the enablement of a method of treating a condition for which an inhibitor of nitric oxide synthase is indicated (see for example the

disclosures in WO 93/13055 to The Wellcome Foundation Limited, WO/98/30537 to Glaxo Group Limited and US Patent No. 6,297,281 to Chabrier de Lassaunier et al. as well as recently provided US Patent No. 5,889,056 to Hodson et al. which teach the use of a Nos inhibitor for the treatment of pain), does not reasonably provide enablement for the prevention of all conditions for which an inhibitor of nitric oxide synthase is indicated nor . Claim 17 recites a method for the "prophylaxis" of a condition and "prophylaxis" is defined by Webster's New World™ Medical Dictionary as the prevention of a disease and therefore claim 17 is interpreted to include the prevention of a condition for which an inhibitor of nitric oxide synthase is indicated. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2nd 1400 (Fed. Cir. 1988) as to undue experimentation.

The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and ,
8) the relative skill of those skilled in the art.

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the art in the assessment of undue experimentation.

1) the nature of the invention; the invention is directed to a method for the treatment and prevention of a condition for which an inhibitor of nitric oxide synthase is indicated.

2) the breadth of the claims; the scope of the method claims includes the prevention of multiple conditions for which an inhibitor of nitric oxide synthase is indicated.

3) the predictability or unpredictability of the art; the ability of preventing multiple conditions for which an inhibitor of nitric oxide synthase is indicated is not yet known in the art. See for example Riedermann et al. Anti-inflammatory strategies for the treatment of sepsis. Expert Opin. Biol. Ther. (2003) 3(2):339-350 which explains that NO has been suggested to exert numerous pro- and anti-inflammatory effects and that high LPS levels and high incidence of multiple organ failure in septic patients have been correlated with elevated serum levels of NO. The reference further states that small clinical trials of two inhibitors were started and one was terminated prematurely when an interim analysis revealed a trend toward a higher mortality rate in the treated group (see page 342-343). The burden of enabling one skilled in the art to prevent all such conditions would be much greater than that of enabling the treatment of such conditions. In the instant case, the specification does not provide guidance as to how one skilled in the art would accomplish the objective of preventing said conditions. Nor is there

any guidance provided as to a specific protocol to be utilized in order to show the efficacy of the presently claimed active ingredients for preventing cancer.

It is the contention that the claim specified actives could actually prevent all conditions including pain and migraine for example, for which an inhibitor of nitric oxide synthase is indicated by simply administering, by any method, an amount of the claim specified active agents. The specification fails to enable one of ordinary skill in the art to practice the presently claimed method for preventing such conditions.

The term "prevention" or "prophylaxis" is synonymous with the term "curing" and both circumscribe methods of treatment having absolute success. Since absolute success is not as of yet reasonably possible with most diseases/disorders, especially those having etiologies and pathophysiological manifestations which are as complex/poorly understood as the types of conditions indicated in the above claims, the specification is viewed as lacking an adequate enablement of where conditions for which an inhibitor of nitric oxide synthase is indicated may be actually prevented, such as pain, migraine etc as claimed in claim 17.

4) the amount of direction or guidance presented; the specification does not provide any guidance in terms of preventing conditions for which an inhibitor of nitric oxide synthase is indicated. Specifically, there are no examples of in vivo data (or in vitro data with a correlative extrapolation to in vivo methods of use) for the method of preventing any condition.

5) the presence or absence of working examples; no working examples are provided for preventing such conditions, for example in a patient, in the specification. The applicant has not provided any competent evidence or disclosed any tests that are highly predictive for the preventative effects of the instant composition or method. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

6) the quantity of experimentation necessary; the quantity of experimentation would be an undue burden to one of ordinary skill in the art and amount to the trial and error type of experimentation. Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention and unpredictability of preventing such conditions, and the lack of working examples regarding the activity and method as claimed, one skilled in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

In consideration of each of factors 1-6, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

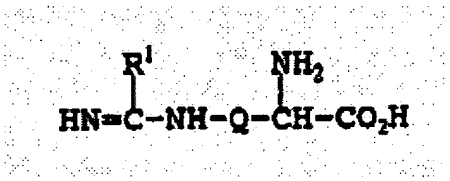
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 8,9,10 and 16-17 are rejected under 35 U.S.C. 102(b) as being anticipate by WO 93/13055 to The Wellcome Foundation Limited.

WO 93/13055 teaches a pharmaceutical composition and methods (see page 1 lines 5-6) comprising (2S)-2-amino-4-{[2-(ethanimidoylamino)ethyl]thio} butanoic acid wherein R^1 is CH_3, Q is $CH_2CH_2XCH_2CH_2$ and X is S of the compound below (see Abstract):



a bulking agent, such as tragacanth (see page 10 line 12), which itself contains small amounts of cellulose and starch (claim 8), and an antioxidant (see page 9 line 30) for the treatment in a human (claims 9 and 16) of a condition where there is an advantage of inhibiting NO production from L-arginine by the action of NO synthase (see page 4 lines 15-20) such as arthritis (claim 10 – see page 5 lines 20-24).

Claim Rejections - 35 USC § 103

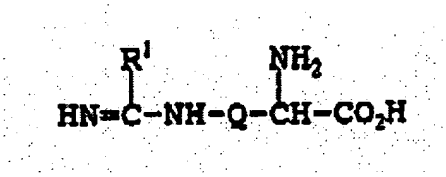
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10 and 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 93/13055 to The Wellcome Foundation Limited in view of WO/98/30537 to Glaxo Group Limited and US Patent No. 6,297,281 to Chabrier de Lassaunier et al.

WO 93/13055 teaches a pharmaceutical composition and methods (see page 1 lines 5-6) comprising (2S)-2-amino-4-{[2-(ethanimidoylamino)ethyl]thio} butanoic acid and a phosphoric acid thereof (claim 2 – see page 8 line 8) wherein R^1 is CH_3, Q is $CH_2CH_2XCH_2CH_2$ and X is S of the compound below (see Abstract):



a bulking agent, such as tragacanth (see page 10 line 12), which itself contains small amounts of cellulose and starch (claim 8), and an antioxidant (see page 9 line 30) for the treatment in a human (claims 9 and 16) of a condition where there is an advantage of inhibiting NO production from L-arginine by the action of NO synthase (see page 4 lines 15-20) such as arthritis (claim 10 – see page 5 lines 20-24).

WO 93/13055 does not specifically teach solvates of (2S)-2-amino-4-{[2-(ethanimidoylamino)ethyl]thio} butanoic acid or any particular chelating agents and amounts thereof or amounts of bulking agents present in the pharmaceutical composition. Nonetheless, given the references below which describe chelating agents, one of ordinary skill in the art would through routine optimization appreciate the composition comprising 0.1 to 5% of the active agent, 80-99.5% of the bulking agent and 0.005 5o 5% of the antioxidant particularly since bulking agents for example are used in higher amounts as a filler (claim 6). In other words, it would be obvious to one skilled in the art to use each additive in an amount appropriate for that additive.

The WO/98/30537 reference teaches the NO synthase inhibitor (2S)-2-amino-4-{[2-(ethanimidoylamino)ethyl]thio} butanoic acid and salts and solvates thereof (claims 2-5 – see page 2 line 26). Although the reference does not recite the particular solvates, mono and trihydrates, absent evidence to the contrary, one of ordinary skill in the art would appreciate the presence of such hydrates from the mention of solvates in the reference.

Chabrier de Lassaunier et al. teach a pharmaceutical composition containing at least one NO synthase inhibiting substance and at least one oxygen reactive form trapping substance (see Abstract) such as those substances with antioxidant properties (see col 2 lines 42-45) and in particular ascorbic acid (claim 7-see col 4 line 40).

One of ordinary skill in the art would have been motivated to combine the above references and as combined would make obvious the invention as claimed. One of ordinary skill in the art would have been motivated to combine WO 98/30537 with WO 93/13055 because WO 98/30537 cites WO 93/13055. One of ordinary skill in the art would have been motivated to combine Chabrier de Lassaunier et al. with WO 98/30537 and WO 93/13055 because Chabrier de Lassaunier et al. teach the combination of at least one NO synthase inhibitor combined with another agent having antioxidant properties and both WO 98/30537 and WO 93/13055 teach No synthase inhibitors and WO 93/13055 teaches the combination of a NO synthase inhibitor combined with an antioxidant as well. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Response to Arguments - 35 USC § 102

Applicant's arguments filed 8 December 2005 have been fully considered but they are not persuasive.

Regarding the rejection under 102(b), the Applicant contends that the reference does not recited the claimed antioxidants and/or chelating agents. The rejected claims,

1, 8,9,10 and 16-17 do not recited any specific agents. Therefore, the cited teachings are commensurate in scope with the claim limitations.

Response to Arguments - 35 USC § 103

Applicant's arguments filed 8 December 2005 have been fully considered but they are not persuasive.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, all three references are directed to a composition which includes the claimed compound and another agent. As shown above, for example, one reference cites the other which alone would direct one of ordinary skill in the art to its teachings, and further wherein both references teach a combined pharmaceutical formulation. To that end, the substitution of one additional agent in lieu of or in addition to a different additional agent taught would have been obvious to one of ordinary skill in the art.

Applicant also contends that the claimed compound is not explicitly recited as a species in the references. Assuming this is a true statement, one of ordinary skill in the art would nonetheless have expected the results and treatment potential taught in the

reference and absent a showing of unexpected results, the claimed method and formulation would have been obvious to one of ordinary skill in the art.

State of the Art

US Patent No. 5,889,056 to Hodson et al. is considered a substantial equivalent to WO 93/13055 to The Wellcome Foundation Limited.

Conclusion

No claim is allowed.

Applicant's amendment (in particular new claim 17) necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Graffeo whose telephone number is 571-272-8505. The examiner can normally be reached 9am to 5:30pm Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

1 February 2006
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